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OFFICE OFPREVENTION,
PESTICIDES AND
TOXIC SUBSTANCES

March 30, 2010

MEMORANDUM

SUBJECT: The Health Effect's Division Re-evaluation of the Fosthiazate/Ethoprop Biomonitoring Surrogacy Issue

PC Code: 129022
Decision No.: NA
Petition No.: NA
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: NA
MRID No.: 45621501, 47811801, 47818801, and 47818802

DP Barcode: D375920
Registration No.: NA
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THROUGH: Felecia Fort, Branch Chief
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TO: Meredith Laws and Rita Kumar
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The fosthiazate registrant, ISK Biosciences has submitted a number of documents proposing the use of an ethoprop biomonitoring data (MRID 45621501) as a surrogate for estimating occupational exposure to fosthiazate. The Agency has repeatedly stated that using the ethoprop biomonitoring data, reflecting use of ethoprop in Pacific Northwest potato fields, as a surrogate for estimating occupational fosthiazate exposure (via internal or external dose surrogation methods) is not recommended (C. Smith, D360902, 1/26/2009; C. Smith and J. Ryman, D368505, 11/19/2009). The Agency maintains this position.

Revised in ink 4/2/2010 CS

The review of MRID 45621501 (Dawson; D281648; 3/1/2005) made clear that the ethoprop biomonitoring data were specific to ethoprop applications to potato fields in the Pacific Northwest. The review specifically stated that, "The conduct of MRID 45621501 was highly focused on the methods, materials, and equipment used by professional applicators in northwest potato fields. For that reason, the results of this study should be considered as **solely** reflective of that applicator population. The design features of MRID 45621501 also reflect this premise."

Background

The initial ISK proposal was to estimate fosthiazate internal dose from the internal dose estimated for ethoprop in the ethoprop biomonitoring study (MRID 45621501). More recently, a new ISK proposal (MRID 47811801) is based on an attempt to calculate ethoprop external dose from the biomonitoring study and then use this value (adjusted for fosthiazate application rate and dermal absorption) to estimate fosthiazate dose. Part of this submission included two protocols for dermal absorption studies (MRID 47818801 and 47818802) which would enable ISK to compare the dermal absorption of fosthiazate and ethoprop. The stated goal of these studies is to derive a refined human dermal absorption factor (DAF) for ethoprop using the Triple Pack approach. The rat *in vitro*/rat *in vivo* ratio for ethoprop would then be used to adjust in vitro dermal absorption data for fosthiazate in human skin to derive a refined human DAF for fosthiazate.

The Agency is aware that ISK Biosciences is proceeding with the proposed fosthiazate and ethoprop dermal absorption studies referenced in the latest submission (MRID 47811801). The Agency continues to believe, for reasons described in detail below that using the ethoprop biomonitoring data as a surrogate for estimating occupational exposure to fosthiazate is not feasible.

- **Application Equipment** – The application equipment used in the ethoprop biomonitoring study is not necessarily representative of the projected equipment used to apply fosthiazate. The ethoprop biomonitoring study included four loader replicates, three applicator replicates, and sixteen loader/applicator replicates. All but four replicates utilized a closed cab tractor coupled with deep shank injection equipment. The other four replicates utilized a specialized groundboom field applicator (e.g., Terragator). Fosthiazate is projected to be applied via groundboom equipment and drip irrigation equipment; not deep shank injection equipment. ISK stated that the Terragator is exactly the type of equipment that would be used in potatoes for fosthiazate. At this time, HED does not have data to demonstrate that it is appropriate to use the shank injection application exposure data from the study to represent groundboom application exposure. The deep shank equipment used in the observational biomonitoring study limits the potential for its generic use and as indicated in the original HED review (Dawson; D281648; 3/1/2005), is indicative of the data being solely representative of the Pacific Northwest potato applicator population.

- **Personal Protective Equipment** – The personal protective equipment (PPE) used in the ethoprop biomonitoring study is not representative of the projected PPE proposed on

fosthiazate labels. In fact, the PPE worn by workers in the ethoprop study exceeded that which was required on the ethoprop product label (as well as that which is required on the proposed fosthiazate labels) for many of the ethoprop biomonitoring study replicates (i.e., gloves and double layers were worn inside enclosed cab tractors). Previous occupational exposure studies have shown that enclosed cabs typically have the biggest impact on reducing exposure but the extra PPE used in the ethoprop study likely had an effect on reducing exposure to ethoprop as well. This effect would certainly be true when applicators exited the enclosed cabs. The use of additional PPE in the ethoprop observational biomonitoring study limits the potential for its generic use and as indicated in the original HED review (Dawson; D281648; 3/1/2005), again points to the focused nature of the study (e.g., quantifying professional applicator exposure during the use of ethoprop in Pacific Northwest potato fields).

- **Use Pattern/Sites** – The use patterns/sites for ethoprop are not necessarily representative of the proposed use patterns/sites for fosthiazate. The ethoprop biomonitoring study was performed with the sole purpose of quantifying professional applicator exposure during the use of ethoprop in Pacific Northwest potato fields. In fact, in the revised ethoprop risk assessment (Dawson; D281648; 3/1/2005), the Agency stated, "...the results of this study should be considered solely reflective of that applicator population." Using the study in a generic sense is not appropriate since the ethoprop study should be considered representative only for the Pacific Northwest potato applicator population. [Note: The Agency is aware that in the past this study was extrapolated to represent exposure resulting from other ethoprop uses that occur outside the Pacific Northwest. HED plans to revisit the use of this study for ethoprop as part of the ethoprop Registration Review process (Farwell; D359595; 12/10/2008).]

- **Physiochemical Differences** – The physiochemical differences between these two pesticides suggest likely differences in absorption, distribution, metabolism, and excretion (ADME), particularly in dermal and inhalation absorption, in mammalian systems.

  - **Dermal Absorption:** With respect to dermal exposure, neither ethoprop nor fosthiazate currently has a guideline dermal absorption study as dermal absorption for both pesticides was estimated. There are major differences in how dermal absorption was estimated for ethoprop (100% - ratio of NOAEL from a 21-day dermal rat study vs. the NOAEL from the comparative ChE study) compared to fosthiazate (20% - ratio of the LOAEL from a 21 day rat dermal toxicity study vs. the LOAEL from a four week dietary rat study). In addition, different vehicles were used in the 21-day dermal studies for ethoprop (4.0% carboxymethylcellulose) and for fosthiazate (corn oil) which would likely affect the rate of dermal absorption. The Agency does not believe it is appropriate to compare these estimated dermal absorption factors.

    ISK agreed with the presented issues related to comparing the estimated dermal absorption factors and submitted two protocols for dermal absorption studies (MRID 47818801 and 47818802). These protocols were revised to reflect the Agency's review of the protocols (C. Smith and J. Rymann, D368505, 11/19/2009). The stated goal of

these studies is to derive a refined human dermal absorption factor (DAF) for ethoprop and fosthiazate using the Triple Pack approach. This issue is important with respect to attempting to surrogate using external dose (e.g., back calculating ethoprop external dose and then adjusting for fosthiazate application rate and dermal absorption).

- **Dermal vs. Inhalation Exposure:** ISK has claimed that the major route of occupational exposure to both ethoprop and fosthiazate is likely to be the dermal route. The Agency maintains that inhalation exposure as well as dermal exposure must be included in any fosthiazate assessment. ISK's external dose method proposal assumes that all ethoprop exposure in the biomonitoring study was from dermal exposure. Data from both PHED and the fosthiazate specific passive dosimetry studies show that the inhalation unit exposures tend to be at least an order of magnitude higher than the dermal unit exposures for engineering control scenarios. It should also be noted that the inhalation point of departure for fosthiazate is two orders of magnitude lower than the dermal point of departure. The combination of these two issues results in inhalation being the risk driver for the fosthiazate handler exposure assessment.

- At the January 2007 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) meeting, the Agricultural Handler's Exposure Task Force (AHETF) presented a comparison of absorbed dose estimates derived from passive dosimetry measurements with those derived from biological monitoring. This comparison included 14 concurrent or consecutive passive dosimetry-biomonitoring studies and 18 different methods of application or reentry scenarios for 8 different active ingredients for which measured human kinetics and dermal absorption data existed. It demonstrated that the total absorbed dose (or daily dosage) estimated using passive dosimetry is generally similar to the measurements for those same scenarios made using human urinary biomonitoring methods. The AHETF concluded that passive dosimetry as a measure of dosage appears to be consistent with biomonitoring with no bias, i.e., there is no tendency to over or under estimate exposure. Based on this analysis, The Agency does not believe that use of data from a surrogate biomonitoring study necessarily outweighs risks that may be estimated using passive dosimetry studies.

Considering the points discussed above, using the ethoprop biomonitoring data as a surrogate for estimating occupational exposure (via internal or external dose surrogation methods) to fosthiazate is not recommended. The Agency maintains that the available passive dosimetry exposure data currently being used to assess fosthiazate exposure is of higher quality and better represents potential fosthiazate exposures than the data found in the ethoprop biomonitoring study. Refinement of the available dermal absorption data for both fosthiazate and ethoprop would not impact the Agency's decision regarding use of the ethoprop biomonitoring study as a surrogate for fosthiazate in anyway. Furthermore, the inhalation exposure pathway would still not be addressed by these studies.

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R181710

Chemical Name: S-sec-Butyl O-ethyl (2-oxo-3-thiazolidinyl)phosphonothioate

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